UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE PROCTER & GAMBLE COMPANY,	:	
Plaintiff,	:	No. 07 Civ. 8379 (RJS)
vs.	:	ECF Case
ULTREO, INC.,	:	
Defendant.	:	

EXPERT REPORT OF ROBERT J. GENCO, D.D.S., PH.D. IN SUPPORT OF PLAINTIFF'S MOTION FOR A PRELIMINARY INJUNCTION

Robert J. Genco, D.D.S, Ph.D., hereby says as follows:

BACKGROUND

1. I am the Vice Provost of Science, Technology Transfer, and Economic Outreach (STOR) at the State University of New York at Buffalo. I have held this position since 2002.

2. I received my dental degree from the State University of New York at Buffalo School of Dentistry ("SUNY Buffalo") in 1963. Following this degree, I attended the University of Pennsylvania, School of Dental Medicine and received a Certificate in Periodontics and a Ph.D. in Microbiology and Immunology in 1967.

3. I have been teaching at SUNY Buffalo since 1968. I continue to teach Microbiology to both dental and medical students and have taught Clinical Periodontology to

dental students and residents in periodontology. In 1990, I was named a Distinguished Professor at SUNY Buffalo.

4. I have served as the President of the American Association of Dental Research, which is the preeminent dental research organization in the United States. I have also served as the President of the International Association for Dental Research. I also am a member of the Institute of Medicine of the National Academy of Sciences.

5. In addition to my work in academia, I have also held a number of positions in various government entities. For example, since 1993 I have been a member of the Over-The-Counter Products Subcommittee of the Dental Products Panel of the Federal Drug Administration, which focuses on the evaluation of products with anti-gingivitis and anti-plaque properties. This subcommittee is commonly referred to as the "plaque subcommittee." I chaired the subcommittee from 1994-1998.

6. I served as the Editor of the Journal of Periodontology and the Annals of Periodontology from 1988 until 2006. Since 1990, I have edited a number of textbooks that are widely used by dental students, including Contemporary Periodontics, Periodontal Medicine and Periodontics: Medicine, Surgery, and Implants.

7. Over the years I have received a number of prestigious awards, including the American Dental Association Gold Medal for Excellence in Dental Research in 1991. This award is only given every three years for excellence in dental research. In 1993, I received the American Academy of Periodontology Gold Medal. Additionally, in 2003, I received the American Dental Association Norton Ross Award, which is given for excellence in clinical dental research. I received this award in recognition of the clinical research I have done over several decades.

8. I am also involved with the establishment of a biotechnology company, named Therex, LLC. Therex is in the process of developing topical drugs for the treatment of gingivitis and acne. The Procter and Gamble Company ("P&G") supported some of the early work done by Therex, but has since withdrawn its support. Therex has applied for and received two currently funded SBIR grants from the National Institute of Health: one for the treatment of gingivitis and the other to study the treatment of acne.

9. Additional details of my background and experience, including a listing of my publications, can be found in my curriculum vitae, which is attached hereto as Exhibit A.

10. Based upon my background and experience, I have extensive experience measuring plaque and gingivitis. I appreciate the need for tight experimental design, randomization and the calibration of examiners in clinical studies designed to measure plaque and gingivitis.

11. I have never testified as an expert witness before in any capacity. I am being paid $375/hour for my time, except for actual attendance at any hearing or trial, where I will be paid $575/hour.

IN VITRO RESEARCH IS NOT NECESSARILY PREDICTIVE OF _IN VIVO_ PERFORMANCE

12. Dental plaque removal studies conducted *in vitro* often cannot be replicated *in vivo*. There are a number of reasons that *in vitro* plaque removal studies are not necessarily accurate predictors of *in vivo* performance.

13. An *in vitro* study using a single strain of bacteria as a model for dental plaque biofilm has limited clinical applications. When bacteria are grown in a culture, they perform differently than bacteria found in the biofilm of the human mouth. Plaque bacteria in the mouth exist in a biofilm where the bacteria clump together to form entangled masses. These

masses form dental plaque, which, by their nature makes them extremely difficult to break up and dislodge. Additionally, bacteria that have formed into biofilms are highly resistant to anti-bacterial agents. Due to the complexity of plaque bacteria, it is difficult to adequately model biofilm *in vitro*.

14. Bacteria cultivated in a culture will grow and perform differently than natural plaque bacteria. Each time the bacteria is divided and cultured, it will grow differently. These differences are magnified the more times the harvested bacteria are grown. When natural plaque bacteria come into contact with other bacteria, they change characteristics in an unpredictable way. This complex interaction among plaque bacteria in the mouth contributes to their unique nature.

15. Newer techniques have determined that there are 300 to 500 types of bacteria found in the human mouth. The types of bacteria vary from person to person, as well as within various regions of the mouth of any given individual. Salivary protein also plays a role in biofilm formation, but that role is not predictable across individuals, or even within a single individual.

16. In studying *in vitro* plaques, a surface must be selected to attach the bacteria. Glass slides or similar artificial surfaces are not adequate. Some studies will use extracted teeth, often from cows, but even these surfaces fail to replicate the actual conditions of the mouth. The surfaces of teeth in the mouth are fully coated with saliva. Additionally, the saliva present in the mouth is constantly renewing itself. On average, fifteen hundred milliliters of saliva proceeds through a human's mouth each day. It is hard to reproduce this surface – with a constantly refreshing stream of saliva passing over each tooth's surface – *in vitro*.

17. When conducting a study of sonic toothbrushes using ultrasonic waves, it is particularly important that the fluid conditions and amount in which the toothbrush is placed accurately reflect the fluids the toothbrush will encounter in actual use in an individual's mouth. Again, it is very hard to model the fluid found in an individual's mouth. The composition of the fluid could vary and include toothpaste, saliva, water and sometimes blood. Additionally, the volume of fluid will not be consistent throughout an individual's mouth, which makes it difficult to design an *in vitro* study that reflects this variation.

"A CLINICAL STUDY EVALUATING THE EFFECTS OF A SONIC TOOTHBRUSH WITH ULTRASOUND WAVEGUIDE IN DISRUPTING PLAQUE WITH AND WITHOUT BRISTLE CONTACT"

18. I have reviewed the clinical study conducted by Aaron Biesbrock, Tao He, Patricia A. Walters and Robert D. Bartizek on the Ultreo toothbrush, entitled "A Clinical Study Evaluating the Effects of a Sonic Toothbrush with Ultrasound Waveguide in Disrupting Plaque with and without Bristle Control." I believe that the study is well designed to evaluate the contribution of the ultrasound component of the Ultreo toothbrush.[1]

19. I know Aaron Biesbrock. He was a graduate student in the Department of Oral Biology at SUNY Buffalo while I was the Director of the Fellowship Program in Immunology and Periodontology in this Department. Although I knew and taught Aaron, I did not serve as his primary Ph.D. mentor.

20. P&G furnished the raw data for this study to the University of Buffalo Periodontology Research Center, which I direct. The analysis conducted at this research center is in substantial agreement with that done by P&G with regard to main treatment effect. Consistent with the P&G findings, I also saw little or no crossover effect in this study.

[1] Attached as Exhibit B is a copy of the study report, executive summary and protocol that I reviewed.

21. The 31 subject population of the study, which used an eight period, four treatment, crossover design, allowed there to be adequate power to determine comparisons between and among the four treatment groups. The power calculations of the study were valid.

22. The study appeared to have adequate randomization since the baseline plaque measurements were evenly balanced between the treatment groups. Baseline plaque measurements are often used to assess randomization.

23. There appears to have been careful quality control methods in place during the study, particularly in relation to the treatment group where a dental hygienist held the Ultreo toothbrush with the ultrasound waveguide three millimeters from surface of the teeth. I understand that the dental hygienist gained experience with the placement of the Ultreo toothbrush for two weeks before the commencement of the study. This quality of this training was further reinforced by a second dental hygienist that observed the placement of the Ultreo toothbrush.

24. One trained and experienced plaque examiner used the Turesky Modified Quigley-Hein Plaque Index to determine the amount of plaque on the subjects' teeth. The use of the Turesky Modified Quigley-Hein Plaque Index is well established for use in clinical studies designed to measure dental plaque removal.

25. The study appeared to be adequately blinded with the plaque examiner having no knowledge of the treatment group of the subject.

26. Data analysis was conducted in a masked fashion using appropriately coded information. Through my discussions with P&G personnel, I learned that the Clinical Trial Manager, Data Manager and statistician were all blinded to the treatment identifiers when they reviewed the data to see if any should be excluded from the analysis. Only after they agree

on the data that will be analyzed does the Data Manager get the treatment codes from the clinical packaging group. In this study, there were no excluded data so all data that were collected at the site were included in the statistical analysis. The statistician then proceeded to follow the analysis plan that was written in the protocol to compare the treatment groups for whole-mouth plaque scores. When they saw no difference between the group where the ultrasound waveguide was held three millimeters from the teeth, and the group that swished the slurry, the statistician conducted supplemental analyses looking at buccal/lingual sites and maxillary/mandibular teeth.

27. The treatment group where the Ultreo toothbrush was used in accordance with operating instructions, and the treatment group where the power of the Ultreo toothbrush was turned off and the toothbrush was used as if it were a manual toothbrush differed in two respects. The power was off in one group and on in the other group. Additionally, there was a difference in brushing instructions given to the two groups.[2] Users of the Ultreo toothbrush were instructed to follow the operating instructions for the Ultreo toothbrush, which provide that the user hold the handle of the toothbrush with a light grip and to try not to press too hard or scrub in order to let the brush do all the work. The operating instructions also direct the user to move the brush in a small circular motion and to spend a few seconds on each tooth before moving to the next tooth. These instructions are not consistent with the common way that an individual uses a manual toothbrush. Despite these two differences between these treatment groups, I believe that that comparisons between these groups are legitimate clinical comparisons. The conclusion that the Ultreo toothbrush worked better with the power off is a statistically significant finding of this study.

28. Although it is difficult to determine the impact of the ultrasound waves beyond where the bristles can reach, the design of this study allows one to conclude that there is

[2] A copy of the brushing instructions given to each of the groups are attached as Exhibit C.

no significant effect of the ultrasound component on plaque removal beyond the reach of the toothbrush bristles. In treatment group three, the tips of the orange side bristles were held just to touch the incisal tooth edge and the gingival margin. This allowed the ultrasound waveguide to be three millimeters from the surface of the teeth, while minimizing any impact for the mechanical application of the bristles.

29. The treatment group where the ultrasound waveguide was held three millimeters from the surface of the teeth removed plaque to the same effect as swishing the dentifrice slurry around in the mouth for one minute. This suggests that the placement of the Ultreo toothbrush with the waveguide three millimeters from the surface of the tooth in fact did not remove any significant amount of plaque based upon any brushing effect since the bristles were not in position to exert significant mechanical effects. The very small amount of plaque removed by the placement of the waveguide three millimeters from the surface of the teeth, or by the swishing of the dentifrice slurry is likely due to the dentifrice slurry or rinsing with the diclosing solution. It appears that the method of delivery of the toothpaste does not significantly impact its effect.

30. The three millimeter distance from the waveguide to the surface of the teeth could allow there to be a fluid interface between the ultrasound waveguide and the tooth surface. A slurry of toothpaste and salvia and possibly water from the toothbrush could have been created that could have mediated the ultrasound waves, especially on the mandibular arch (*i.e.*, lower teeth). The fact that there was no difference determined between the mandibular (lower) and maxillary (upper) arches indicates again that there is no effect of the ultrasound waves beyond the toothbrush bristles.

31. The lack of dental plaque removal as reported in the study conducted by Aaron Biesbrock, *et al.*, is consistent with the study conducted by Jenkins, W., Wei, J., Mortis, K., and Strate, J., entitled "Comparison of plaque removal by Sonicare FlexCare, Ultreo and Ultreo with ultrasound disabled," obtained from the Sonicare website.[3] However, the Jenkins *et al.* study is only presented in abstract form and cannot be critically evaluated for methodology.

32. Finally, the Biesbrock, *et al.* study has been accepted for publication in The American Journal of Dentistry, a peer-reviewed journal. This acceptance demonstrates that the study met the criteria for design, implementation and analysis of a widely-accepted scientific journal.

ULTREO'S STUDIES

33. I have looked at the abstracts of Ultreo's own studies of the Ultreo toothbrush from the Ultreo website. I have also looked at "Efficacy and Safety of a New Power Toothbrush in a Population with Mild to Moderate Gingivitis," in The Journal of Clinical Dentistry, which is the only published clinical study on the Ultreo toothbrush of which I am aware. I do not see any results that would support the conclusion that the ultrasound component of the Ultreo toothbrush generates or activiates bubbles in the mouth that are able to remove plaque bacteria.

34. I have considered the abstract of a small pilot study, "Comparison of Ultreo to a manual toothbrush and floss in ability to remove dental plaque," conducted by Baltuck, C., Ortblad K and McInnes, C. and is reported on the Ultreo website. Ultreo reports that this study showed a significant difference in the change in interproximal plaque formation over time compared to subjects using the manual toothbrush and floss. However, this abstract also reports that there was no overall difference between the use of the Ultreo and the use of the

[3] A copy of this abstract is attached as Exhibit D.

manual toothbrush and floss when the data from the entire two week study was combined. It is unclear how to reconcile these two findings. Additionally, I have only been able to review a short abstract and protocol of this study, which limits my ability to critically analyze the study, including information regarding experimental design, the standard deviation, the statistical power of the study and whether there were any carryover or period effects that would impact the results. Moreover, I have no information regarding compliance issues, such as whether the subjects were supervised while using the floss, which is critical for any study using floss since it is well known that individuals are not generally effective at flossing. Even if the result reported by Ultreo is an appropriate finding of this study, this does not demonstrate that ultrasound waves are responsible for the interproximal plaque reduction. The reduction could be attributed to a number of other factors, including the design of the brush and bristles. Without a control of the ultrasound disengaged, it would be difficult to isolate that effect.

35. I also have considered the published study, "Efficacy and Safety of a New Power Toothbrush in a Population with Mild to Moderate Gingivitis," in The Journal of Clinical Dentistry and do not believe that this study demonstrates that the ultrasound or the bubbles generated or activated by the ultrasound remove plaque bacteria. Again, there was no control used of the Ultreo toothbrush with the ultrasound disengaged. Moreover, there were no measurements taken of interproximal plaque or of plaque in other hard-to-reach areas. Instead, the measurements taken were of gingivitis reduction in the mouth overall.

36. I also have considered the abstract of the study, "Efficacy of Ultreo in dental plaque removal," conducted by Sharma, N.C., Qaqish, J., Galustians, J. and Ortblad, K., which is available on the Ultreo website. This clinical study involved a comparison of the Ultreo toothbrush after one minute of use against the Ultreo toothbrush after two minutes of use.

Although the abstract reports that there was plaque reduction seen after both one and two minutes, both in the entire mouth and in interproximal areas, this study fails to demonstrate why there was a reduction in plaque. It cannot be concluded from this clinical study whether the plaque reduction came from the design of the brush and the bristles or whether the ultrasound had any contribution to plaque reduction. Again, my analysis of this study is hindered by the fact that I have only been able to review an abstract of the study.

37. I also considered the abstract of the clinical study, "Evaluation of probing depth and bleeding in an in-office setting," conducted by Lee, V.M., Harrison, A.W., Bagnulo, M.A., and Zappone, A.M., which is found on the Ultreo website. I do not believe that this study demonstrates that the ultrasound or the bubbles that the ultrasound may create or activate remove plaque bacteria in hard-to-reach areas. The reduction in probing depth and bleeding could be attributed to a number of factors, including the design of the brush and bristles, as well as simply the resolution of surface inflammation of the gingival tissue. Again, my analysis of this study is hindered by the fact that I have only been able to review an abstract of the study.

38. I also have considered the abstract of the *in vitro* study, "Evaluation of ultrasound as a means to remove *Streptococcus mutans* biofilm," conducted by Roberts, F.A., Hacker, B., Oswald, T., McInnes, C., which is available on the Ultreo website. While the results of this *in vitro* study may be interesting to a company developing a product, it is unlikely that I would have published such a study in any of the journals that I edited. Instead, I would have insisted on clinical data to confirm the results of the *in vitro* test. While the *in vitro* test showed that some bacteria was removed from a test-tube environment, one does not know if these results are transportable or relevant to actual use, given the unique nature of the human mouth.

39. Additionally, I have further concerns regarding the Roberts, *et al.*, *in vitro* study. There are three main differences between the *in vitro* model used in the Roberts study and the oral cavity which could impact whether the results could be replicated *in vivo*. First, the surfaces on which the bacteria are grown – frosted glass slides and hydroxyapatite discs – are not equivalent to teeth in the mouth for the purpose of measuring plaque removal. Teeth in the mouth are covered with salivary pellicle and are either enamel, cemented covered dentin or dentin exposed by deep scaling (in a patient suffering from deep scaling). As I discussed above, the surface on which the bacteria are placed impacts its ability to adhere and react to pressures. Second, a single bacteria does not have the characteristics of a complex biofilm. *In vivo* biofilms vary widely among individuals and in various sites within any given individual's mouth. Biofilms are comprised of an indeterminate number of the 300-500 bacteria that are known to populate the oral cavity. Moreover, once a biofilm forms dental plaque, it is much more difficult to remove and break apart than a single bacteria. The third difference is the fluid used. In the *in vitro* experiment, a dentifrice slurry was used, but the contents and amount of this slurry were not disclosed. In the mouth, a combination of dentifrice and salvia are presented, which may be diluted by the presence of water from the toothbrush. The volume of fluid may also vary from *in vitro* to *in vivo*. These differences could account for the finding *in vitro* that Ultreo tends to remove *S. mutans* from grooved glass slides, where the other two tested toothbrushes appeared to have a lesser effect. These differences also preclude predicting whether the same results would appear *in vivo*. There is no way, based upon this study, to know whether the ultrasound would be effective at removing plaque in hard-to-reach areas of the human mouth *in vivo*. Simply put, the ultrasound function of the Ultreo toothbrush may be better at removing a single bacteria, *S. mutans*, from an artificial surface in an artificial slurry than other toothbrushes, but one cannot

conclude that the ultrasound function will be able to remove complex dental plaque on actual teeth (in hard-to-reach areas) in the fluid found in the oral cavity

40. I have conducted a search for other clinical studies that could support the conclusion that the ultrasound or the bubbles that it may create or generate are able to remove plaque bacteria in the mouth, but was not able to find any such clinical studies.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed this 24th day of November, 2007.

Robert J. Genco, D.D.S., Ph.D.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing was served electronically by the Court's ECF system pursuant to the rules of this court.

Dated December 12, 2007

s/ Laura W. Sawyer
Laura W. Sawyer